REMARKS

The present application relates to a method of identifying compounds which resensitize cancer cells to the effects of chemotherapeutic agents. The chemosensitizing compounds identified by said method do not necessarily have the cytotoxic effects of chemotherapeutic agents. In particular, the chemosensitizing compounds identified by said method of identifying compounds may be further used in combination with chemotherapeutic agents.

Applicants request reconsideration and allowance of the application in light of the foregoing amendments and the following remarks.

Claims 64-69 are pending in the application. Claim 66 has been amended and claims 64-65, and 68-69 have been canceled.

In the Office Communication of April 17, 2004 the Examiner has rejected claims 64-69 under 35 USC 112 first paragraph as failing to adequately teach how to make and/or use the invention, and thereby failing to provide an enabling disclosure.

The Examiner has further rejected claims 64-69 wherein the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Applicants believe the rejection can be withdrawn in view of amended claim 66 and cancelled claims 64-65 and 68-69.

In response, applicant believes they have complied with 35 USC 112 first paragraph by amending claim 66. Applicants believe that the specification including the testing procedures in the present application enable the invention within the meaning of 35 USC 112 and provide clear guidance. Further, compounds have been identified, using methods described in the specification, as those exemplified by those of Formula (I), Fumitremorgin A, Fumitremorgin B, and Fumitremorgin C.

As presented in the specification on page 3, lines 34-35, "An important aspect of this invention is the capability to identify test compounds as chemosensitizing agents following evaluation in an assay of this invention." Applicants have further identified, using the assay as a means of identifying the chemosensitizing compounds in amended claim 66 as those of Formula (I), Fumitremorgin A, Fumitremorgin B, and Fumitremorgin C when contacted with cell line S1-M1-3.2.

As an illustration of testing procedures and test results are those described in the specification and in Table 14 on page 33 where the test results of resensitizing S1-M1-3.2 Human Colon Cancer Cells to Mitoxantrone and Toxicity of Fumitremorgin A, B and C and Diketopiperazines against S1-M1-3.2 are presented. The concentration of compounds, Fumitremorgin A, B, C and examples of Formula (I) at the doses described (μM) are toxic doses which kill more than 20% of the cells. When the same compounds are given with Mitoxantrone where the concentration of compound that kills 50% of the cells is less than the

toxic doses which identifies these compounds as resensitizing the cells to the chemotherapeutic effects of Mitoxantrone.

To further illustrate the above, the ability of FTC to resensitize S1-M1-3.2 cells to mitoxantrone is shown in Table 7 where cells were incubated for three days with the indicated doses of FTC alone or in combination with 3.2 μM mitoxantrone. Cell survival is estimated using the SRB assay described on page 18 of the specification.

No toxicity of FTC alone was observed in the dose range tested (0.1-80μM). However, in combination with mitoxantrone, 50% of the cells were killed with 0.35 μM of the drug.

In further illustration of the test procedures and results with further antitumor agents the Examiner's attention is drawn to Table 10, in the specification on pages 27-28, where multiple antitumor agents are tested with the chemosensitizing compound FTC in multiple cell lines wherein the test data show an increase in reversal activity with mitoxantrone(93 fold), doxorubicin(26 fold) and topotecan(24 fold).

Applicants believe they have provided sufficient working examples.

Based on the foregoing, it is respectfully submitted that the present application contains more than sufficient description to enable the skilled artisan to carry out the method set forth in the amended claims without undue experimentation. Accordingly, withdrawal of the section 112 rejection is respectfully urged.

It is respectfully submitted that the claims 66-67 in view of the experimental description and illustrated testing procedures and results in the specification are allowable.

The Examiner has additionally rejected claims 64-69 under 35 USC 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants believe they have complied with 35 USC 112 second paragraph by the amendments to claim 66. In particular, in amended claim 66 chemosensitizing compounds have been identified as those of Formula (I), Fumitremorgin A, Fumitremorgin B, and Fumitremorgin C.

Based on the foregoing, it is respectfully submitted that the present amended claims, clearly point out and distinctly claim the invention. Definition of the chemosensitizing compounds as those within the generic of Formula (I), Fumitremorgin A, Fumitremorgin B, or Fumitremorgin C overcome the indefinite rejection. Accordingly, applicants believe they have complied with 35 USC 112 second paragraph by amendments to claim 66. Applicants respectfully ask the Examiner to reconsider and withdraw the rejection.

The Examiner has rejected claims 64-67 under 35 U.S.C. § 102(b) as anticipated by Parekh et al. This rejection is respectfully traversed in view of amended claim 66. The cell lines described by Parekh et al are CML leukemic cell lines which express p-glycoprotein. The authors describe the use of quinidine to resensitize the CML cells to mitoxantrone and adriamycin. In the instant invention, the colon cell line S1-M1-3.2 is used and is considerably different from the CML cell line of the Parekh et al reference abstract. The CML and S1-M1-3.2 cell lines are from different tissues and have different mechanisms of

resistance. In particular, the S1-M1-3.2 cell line expresses BCRP. Applicants respectfully request the Examiner to withdraw the rejection in view of the above remarks.

Finally claims 64-69 are rejected under 35 U.S.C § 103 as being unpatentable over Parekh et al, and Naito et al in view of the Merck Manual. This rejection is respectfully traversed, especially in view of amended claim 66.

The Merck Manual points to combination therapies of anticancer drugs. However, there is no teaching in Merck that would point to the problem solved by the instant invention. In the instant invention, the resensitizing compounds Formula (I), Fumitremorgin A, Fumitremorgin B, and Fumitremorgin C, which are not anticancer agents at the doses used, are used in combination with anticancer agents.

The instant invention is simply not a mixing or combination of two neoplastic agents. What the invention is however, is a method to identify chemosensitizing compounds, which resensitize cancer cell lines, in particular S1-M1-3.2 which have enhanced resistance to chemotherapeutic agents and in particular to chemotherapeutic agents selected from mitoxantrone, doxorubicin, and topotecan.

Importantly, exemplified Fumitremorgin A, B and C and the diketopiperazines of Formula (I) are not chemotherapeutic agents at the dose used.

The Naito et al reference does not solve the problem that is solved by the instant invention. The Naito et al reference however describes an atypical cancer cell line resistant to adriamycin and the analysis of the decreased cellular level of DNA Topo II and an overexpression of MRP gene. The Naito et al art does not suggest that it would be desireable to develop a method for identifying a chemosensitizing compound of the instant invention.

The Cui et al reference describes the preparation of new diketopiperazine derivatives produced by the fungus Aspergillus fumigatus which includes fumitremorgin C. However, the Cui et al art does not suggest that it would be desireable to develop a method of identification of the chemosensitizing compounds described in the instant invention.

As described by the Examiner, "it is generally considered prima facie obvious to combine compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose."

In response, applicants have not combined compounds taught in the prior art to be useful for the same purpose. Applicants have however, discovered through the method of identification of the invention which chemosensitizing compounds can be combined with chemotherapeutic agents to enhance the ability of the antitumor agents to increase cell death in cells which have drug resistance.

The Examiner cited art of the Merck Manual, Naito et al and Parekh et al do not suggest, teach or provide guidance as to the method of identification described herein in amended claim 66 or in claim 67.

It is the applicants view that the Merck Manual, Naito et al and Parekh et al neither anticipate nor render obvious the presently claimed invention. Applicant respectfully requests the Examiner to reconsider and withdraw the Section 103 rejection.

In conclusion, applicants respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein, amendments to the claims, and allow the application. Favorable treatment is earnestly solicited.

Respectfully submitted,

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